Occupation and Risk of Pancreatic Cancer: A Population-Based Case–Control Study in Iowa

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Objective: Previous epidemiological studies have inconsistently linked various occupations and industries to pancreatic cancer risk. ***Methods:*** *We analyzed data from a population-based case–control study conducted in Iowa involving 376 histologically confirmed incident pancreatic cancer cases and 2434 control subjects.* ***Results:*** *A significantly increased risk was observed among men who worked in the following industries: chemical and allied products, transportation, and elementary and secondary schools. Increased risks also were observed in men who were employed as truck drivers; railroad brake, signal, and switch operators; purchasing agents and buyers; teachers; insurance agents; and retail supervisors. Among women, a significantly increased risk of pancreatic cancer was found for employment in furniture and home furnishing stores, and a borderline significantly increased risk among textile sewing machine operators and tenders.* ***Conclusions:*** *Working in several occupations and industries was associated with an increased risk of pancreatic cancer in this study, and these associations warrant further investigation.* (J Occup Environ Med. 2005;47: 392–398)

Pancreatic cancer is a rapidly fatal malignancy.[1–4] It is the fourth-leading cause of cancer-related deaths in the United States.[1,4] Smoking is considered to be the only established nonheritable risk factor for pancreatic cancer, but smoking explains no more than 30% of the cases.[1,4]

Various industries and occupations have been linked to pancreatic cancer risk, although findings have been inconsistent. Some studies have suggested an increased risk of pancreatic cancer among men and women who worked in chemical industries[5–8] whereas others do not.[9,10] Employment in metals industries also has been associated with an increased risk of pancreatic cancer in some studies,[9,11–13] although not others.[14] Working in the rubber[10,13–15] and printing[9,16–18] industries, as well as working as a leather tanner,[8,10,14,19] glass manufacturer,[10,13] and mechanic[9,20–22] also have been inconsistently associated with a risk of pancreatic cancer. To further examine the relationship between industrial and occupational exposures and risk of pancreatic cancer among both men and women, we analyzed data from a population-based case–control study of pancreatic cancer in Iowa.

Materials and Methods

Study Population

A detailed description of the population has been described elsewhere.[23] Briefly, all eligible incident cases were identified through the State Health Registry of Iowa and diagnosed between August 1985 and

December 1987. All cases who were histologically confirmed as having pancreatic adenocarcinoma were aged between 40 and 85 years and were residents of Iowa. In addition, they had no previous diagnosis of a malignant neoplasm except for non-melanoma skin cancer. A total of 376 pancreatic adenocarcinoma cases participated (202 males and 174 females) in this study. The overall response rate was 88%. These cases were part of a larger study that also included cancers of the bladder, kidney, brain, colon, and rectum.

Control subjects were frequency-matched by gender and 5-year age groups to all cases in the larger study. Control subjects were selected randomly from computerized state driver's license records for persons younger than age 65 and from the U.S. Centers for Medicare & Medicaid Services (CMMS) listings for ages 65 and older. Persons with a previous cancer diagnosis, other than nonmelanoma skin cancer, were excluded from consideration as control subjects. A total of 2434 population-based control subjects (1601 males and 833 females) were recruited in this study, with participation rates of 82% for controls younger than 65 and 79% for those aged 65 or older.

Data Collection

Information was collected from subjects or next-of-kin using mailed questionnaires supplemented by telephone interviews. Of the 376 case respondents, 339 (90.2%) were proxies, including 189 (56%) spouses, 23 (7%) siblings, 99 (29%) children, and 28 (8%) others. When more than one proxy participated, these numbers are presented with priority in the following order: spouse, sibling, off-spring, and other. Of the 2434 population-based controls, 243 (10%) respondents were proxies, with 179 (74%) spouses, 13 (5%) siblings, 32 (13%) children, and 19 (8%) others. Respondents were asked to report all jobs held for at least 5 years since age 16. Information for each job included job title, the type of busi-ness or industry, the years when each job began and ended, and the activities and duties associated with the job. Industries and job titles were coded according to schemes of the 1987 edition of the Standard Industry Classification (SIC)[24] and the 1980 Standard Occupational Classification Manual (SOC).[25] Information on demographic factors, smoking, past medical histories, first-degree family history of pancreatic cancer and other cancers, and dietary patterns also were collected.

Data Analysis

Unconditional logistic regression models were used to calculate odds ratios (ORs) for pancreatic cancer associated with jobs for males and females separately. For each sex, ORs were calculated for all two-digit, three-digit, and four-digit SOC and SIC codes when there were at least four or more exposed cases. We also evaluated the risk of pancreatic cancer by duration of employment (<10 years and ≥ 10 years) in various SOC and SIC categories. The reference category was composed of subjects not employed in the occupation or industry of interest.

The following potential confounders, which showed an impact on the observed ORs, were included in the final regression models: age (40–54, 55–64, 65–74, 75–85 years), red meat intake (quartile), fruit intake (quartile), leisure time physical activity (≥ 1/day, 2–6/week, 1–4/month, <1/month), having a first-degree relative with pancreatic cancer (yes/no), and tobacco smoking (ever/never). Ever smokers included people who ever smoked cigarettes, cigars, or pipes, or chewed tobacco products. To control for possible residual confounding from smoking, the duration of smoking in years was included in the final model. Additional adjustment for education level and other types of cancer in first-degree relatives did not change the observed associations. These factors were not included in the final models.

Results

Table 1 presents the distribution of selected baseline characteristics for cases and control subjects. Age was not evenly distributed between the cases and controls and was therefore included in the final regression models. Compared with controls, cases were more likely to have consumed red meat and have smoked cigarettes but were less likely to have had leisure-time physical activity. Female cases and male control subjects were less likely to have consumed fruits compared with female controls and male cases, respectively. Among both men and women, a higher proportion of cases than controls reported having a first-degree relative with pancreatic cancer.

Table 2 presents associations in which the risk estimates were equal to or larger than 2.0, either overall or in one of the duration categories, for pancreatic cancer among males by industry and occupation using two-, three- or four-digit SIC and SOC codes. A significantly increased risk was observed among men who worked in the chemical and allied product industries, railroad transportation industries, trucking and warehousing, and elementary and secondary schools. Risk of pancreatic cancer was greater for duration of employment of ≥ 10 years than <10 years, except for trucking and warehousing.

A not significant increase in risk of pancreatic cancer was observed for men who worked in transportation equipment industries, communications industries, eating and drinking places, and miscellaneous retail establishments, as well as insurance carriers. Men employed as purchasing agents and buyers, as teachers, and as railroad brake, signal, and switch operators also experienced a significantly increased risk, and the risks were greater among those with ≥ 10 years' employment than with fewer years in these occupations. An increased risk also was observed among men employed as sales occu-

TABLE 1
Pancreatic Cancer Cases and Controls by Selected Characteristics

	Men		Women	
	Case (%)*	Control (%)*	Case (%)*	Control (%)*
Factor				
Age (years)				
40–54	24 (11.8)	149 (9.3)	6 (3.5)	93 (11.2)
55–64	62 (30.7)	358 (22.4)	30 (17.2)	190 (22.8)
65–74	68 (33.7)	629 (39.3)	68 (39.1)	276 (33.1)
75–85	48 (23.8)	465 (29.0)	70 (40.2)	274 (32.9)
Red meat intake (servings/year)				
<299	12 (7.9)	283 (21.7)	28 (21.4)	229 (34.5)
299–436	32 (21.2)	313 (24.0)	34 (25.9)	175 (26.4)
437–637	48 (31.8)	337 (25.8)	41 (31.3)	155 (23.4)
>637	59 (39.1)	371 (28.5)	28 (21.4)	104 (15.7)
Unknown	51	297	43	170
Fruit intake (servings/year)				
<431	29 (20.0)	345 (27.3)	26 (20.5)	101 (15.4)
431–588	34 (23.4)	338 (26.7)	40 (31.5)	141 (21.6)
589–858	31 (21.4)	295 (23.3)	26 (20.5)	195 (29.9)
>858	51 (35.2)	287 (22.7)	35 (27.5)	216 (33.1)
Unknown	57	336	47	180
Leisure time physical activity				
≥1/day	42 (24.6)	281 (19.3)	33 (21.4)	160 (22.2)
2–6/week	32 (18.7)	402 (27.7)	36 (23.4)	249 (34.6)
1–4/month	23 (13.4)	216 (14.9)	18 (11.7)	132 (18.3)
<1/month	74 (43.3)	553 (38.1)	67 (43.5)	179 (24.9)
Unknown	31	149	20	113
Tobacco smoking				
Never	34 (16.8)	445 (27.8)	91 (52.3)	574 (68.9)
Ever	168 (83.2)	1156 (72.2)	83 (47.7)	259 (31.1)
First-degree relatives with pancreatic cancer				
No	174 (95.1)	1496 (98.5)	142 (91.6)	778 (97.3)
Yes	9 (4.9)	22 (1.5)	13 (8.4)	22 (2.7)
Unknown	19	83	19	33

*Listed percentages do not include persons with unknown values.

pation supervisors, in insurance sales occupations, and service occupations (except for private households and protective), especially for food and beverage preparation, as well as heavy truck drivers.

The percentage of smokers among male cases who were employed in the aforementioned industries and occupations ranged between 73% and 100%. After restricting the analysis to smokers, no important changes were noted in the magnitude of most observed associations, although some of the associations became not significant including railroad transportation industries and railroad brake, signal, and switch operators (data not shown).

Table 3 presents associations for which the OR is ≥2.0, either overall or in one of the duration categories by industry and occupation for females. Women who had worked in furniture and home furnishings stores experienced a fivefold increased risk. Women employed as officials and administrators or textile sewing machine operators and tenders also experienced an increased risk of pancreatic cancer, and the risk was higher among those employed ≥10 years than fewer years. An excess of pancreatic cancer risk also was observed among women who worked in executive offices, legislative bodies, and general government and for those employed as service organization managers, sales workers, waitresses, farm operators and managers, and assemblers. Among these associations, the only signifi-

cantly high risks were among furniture and home furnishing retail workers. There was only one case who worked in a furniture and home furnishings store and three cases who were employed as textile sewing machine operators and tenders who were smokers (data not shown).

Discussion

In this population-based case-control study, we found an increased risk of pancreatic cancer among men who worked in chemical and allied products industries, and railroad transportation industries, specifically men who worked as railroad brake, signal, and switch operators. Women who had worked as textile sewing machine operators and tenders and in the furniture and home furnishings

TABLE 2
Risk (≥ 2.0) of Pancreatic Cancer by Industry or Occupation in Men (Based on 4 or More Exposed Cases)

Industry	Ca/Co	OR (95% CI)†	OR (95% CI)*	<10 Years Ca/Co	OR (95% CI)†	OR (95% CI)*	≥10 Years Ca/Co	OR (95% CI)*	OR (95% CI)†
Industry (SIC code)									
Chemicals and allied products (28)	6/17	2.9 (1.1–7.3)	3.5 (1.3–9.2)	1/6	1.3 (0.2–11.2)	1.5 (0.2–13.0)	5/11	3.7 (1.3–10.7)	4.7 (1.5–14.3)
Transportation equipment (37)	4/18	1.8 (0.6–5.3)	1.8 (0.6–5.8)	2/5	3.1 (0.6–16.6)	5.5 (1.0–31.3)	2/13	1.2 (0.3–5.5)	1.0 (0.2–4.8)
Railroad transportation (40)	11/33	2.7 (1.4–5.5)	4.1 (2.0–8.6)	1/9	0.9 (0.1–7.2)	1.4 (0.2–11.5)	10/24	3.4 (1.6–7.3)	5.1 (2.3–11.5)
Trucking and warehousing (42)	9/56	1.3 (0.6–2.6)	1.1 (0.5–2.4)	5/11	3.6 (1.3–10.6)	3.3 (1.1–10.1)	4/45	0.7 (0.3–2.0)	0.6 (0.2–1.8)
Trucking and courier services except by air (421)	4/15	2.1 (0.7–6.5)	2.3 (0.7–7.2)	3/7	3.4 (0.9–13.4)	3.7 (0.9–15.6)	1/8	1.0 (0.1–8.0)	1.0 (0.1–8.7)
Communications (48)	4/16	2.0 (0.7–6.0)	2.0 (0.6–6.1)	0/2			4/14	2.3 (0.7–7.0)	2.2 (0.7–7.1)
Eating and drinking places (581)	4/28	1.1 (0.4–3.3)	1.2 (0.4–3.7)	2/6	2.6 (0.5–13.2)	2.5 (0.5–13.1)	2/22	0.7 (0.2–3.1)	0.8 (0.2–3.7)
Miscellaneous retail (59)	5/30	1.3 (0.5–3.5)	1.7 (0.6–4.6)	0/9			5/21	1.9 (0.7–5.1)	2.4 (0.9–6.8)
Insurance carriers (63)	6/29	1.7 (0.7–4.0)	2.2 (0.9–5.6)	1/7	1.1 (0.1–9.4)	1.5 (0.2–13.0)	5/22	1.8 (0.7–4.9)	2.4 (0.9–6.8)
Elementary and secondary schools (8211)	5/20	2.0 (0.7–5.4)	2.3 (0.8–6.5)	0/6			5/14	2.9 (1.0–8.0)	3.4 (1.1–10.1)
Occupation (SOC code)									
Purchasing agents and buyers (144)	4/15	2.1 (0.7–6.5)	2.3 (0.7–7.3)	0/5			4/10	3.2 (1.0–10.3)	4.1 (1.2–14.7)
Teachers (224)	4/13	2.5 (0.8–7.6)	2.9 (0.9–9.9)	0/3			4/10	3.2 (1.0–10.3)	4.2 (1.2–14.7)
Supervisors; sales occupations, retail (403)	15/70	1.8 (1.0–3.1)	2.1 (1.2–3.9)	8/16	4.1 (1.7–9.7)	5.4 (2.2–13.6)	7/54	1.1 (0.5–2.4)	1.2 (0.6–2.3)
Insurance sales occupations (4122)	4/7	4.6 (1.3–15.9)	5.5 (1.5–20.1)	2/0			2/7	2.3 (0.5–11.1)	2.6 (0.5–13.7)
Service occupations, except private household and protective (52)	10/66	1.2 (0.6–2.4)	1.4 (0.7–2.9)	6/21	2.3 (0.9–5.7)	2.7 (1.0–7.1)	4/45	0.7 (0.3–2.0)	0.8 (0.3–2.4)
Food and beverage preparation and service occupation (521)	4/15	2.1 (0.7–6.5)	2.3 (0.7–7.4)	3/6	4.0 (1.0–16.1)	3.8 (0.9–16.7)	1/9	0.9 (0.1–7.1)	1.1 (0.1–9.1)
Truck drivers, heavy (8213)	11/58	1.5 (0.8–3.0)	1.3 (0.7–2.6)	5/13	3.1 (1.1–8.8)	3.3 (1.1–9.9)	6/45	1.1 (0.5–2.6)	0.9 (0.3–2.1)
Railroad brake, signal, and switch operators (8233)	4/8	4.0 (1.2–13.5)	5.9 (1.7–21.0)	1/2	4.0 (0.4–44.6)	5.3 (0.5–62.2)	3/6	4.0 (1.0–16.2)	6.1 (1.4–26.6)

*Crude odds ratio.
†djusted for age, physical activity, smoking, red meat intake, fruit intake, and first-degree relative with pancreas cancer

TABLE 3
Risk (≥2.0) of Pancreatic Cancer by Industry or Occupation in Women (Based on 4 or More Exposed Cases)

Industry	Ca/Co	OR (95% CI)*	OR (95% CI)†	<10 Years Ca/Co	OR (95% CI)*	OR (95% CI)†	≥10 Years Ca/Co	OR (95% CI)*	OR (95% CI)†
Industry (SIC code)									
Furniture and home furnishings stores (57)	4/3	6.5 (1.4–29.3)	5.5 (1.1–27.3)	0/0			4/3	6.5 (1.4–29.3)	5.1 (1.1–27.3)
Executive, legislative, and general government (91)	4/12	1.6 (0.5–5.1)	1.2 (0.3–4.0)	3/4	3.6 (0.8–16.3)	4.2 (0.7–23.5)	1/8	0.6 (0.1–4.9)	0.3 (0.0–2.9)
Occupation (SOC code)									
Officials and administrators (12,13)	8/23	1.2 (0.5–2.7)	1.3 (0.5–3.1)	1/17	0.3 (0.0–2.1)	0.3 (0.0–2.2)	7/15	2.3 (0.9–5.6)	2.5 (0.9–7.0)
Managers, service organizations (135)	4/9	2.2 (0.7–7.1)	1.2 (0.3–4.6)	1/5	1.0 (0.1–8.4)	0.4 (0.0–3.6)	3/4	3.6 (0.8–16.4)	3.5 (0.6–21.1)
Sales occupations, other (436)	5/14	1.7 (0.6–4.9)	2.0 (0.7–6.2)	3/4	3.6 (0.8–16.4)	4.3 (0.9–21.3)	2/10	1.0 (0.2–4.5)	1.1 (0.2–5.6)
Waitresses (5213)	4/16	1.2 (0.4–3.6)	1.1 (0.3–3.8)	1/10	0.5 (0.1–3.8)	0.4 (0.0–3.2)	3/6	2.4 (0.6–9.7)	3.1 (0.6–14.9)
Farm operators and managers (55)	4/9	2.2 (0.7–7.1)	2.4 (0.7–9.4)	1/1	4.8 (0.3–77.9)	6.3 (0.3–136.5)	3/8	1.8 (0.5–6.9)	2.0 (0.5–8.1)
Textile sewing machine operators and tenders (7655)	4/5	3.9 (1.0–14.7)	3.9 (1.0–15.5)	1/2	2.4 (0.2–27.0)	2.0 (0.2–23.0)	3/3	4.9 (1.0–24.3)	5.6 (1.0–31.4)
Assemblers (772)	4/13	1.5 (0.5–4.6)	1.7 (0.5–5.7)	3/5	2.9 (0.7–12.2)	3.7 (0.7–18.3)	1/8	0.6 (0.1–4.9)	0.6 (0.1–5.4)

*Crude odds ratio.
†djusted for age, physical activity, smoking, red meat intake, fruit intake, and first-degree relative with pancreas cancer.

retail industry also were at elevated risk.

Previous epidemiological studies reported an increased risk of pancreatic cancer associated with working in the chemical industries, with inconsistent findings. In a mortality study involving 3637 deaths from the American Chemical Society between 1948 and 1967, Li et al[5] reported a significantly higher proportion of deaths from pancreatic cancer among male chemists aged 20–64 years ($P < 0.01$) compared with professional men in general. In standardized mortality ratio (SMR) studies, Hanis et al[6] reported a nonsignificantly increased risk of pancreatic cancer (SMR = 152) among refinery and chemical plant workers, and Bond et al[7] also reported a nonsignificantly increased risk of pancreatic cancer (SMR = 233) among chemical workers. A case–control

study using death certificates, involving 343 pancreatic cancer deaths and 1315 other deaths as controls, observed an OR of 1.4 for people working in the chemical and allied industries.[8] In a case–control study including 625 pancreatic cancer cases and 1700 other cancer controls, Partanen et al[9] reported a slightly reduced risk of pancreatic cancer associated with employment in the chemical and allied industries. In a nested case–control study involving 28 pancreatic cancer deaths and 140 randomly selected controls, Selenskas et al[26] observed an increased risk of pancreatic cancer associated with processing vinyl and polyethylene. Another nested case-control study by Garabrant et al,[27] involving 28 pancreatic cancer deaths and 112 matched controls reported that exposure to DDT was associated with an increased risk of pancreatic cancer.

An increased risk of pancreatic cancer associated with working in chemical industries is biologically plausible because many chemical agents have been suggested as carcinogens and some of them have been shown to increase the risk of pancreatic cancer. For example, aromatic amines,[28] stabilizers in vinyl processing (such as barium-cadmium laureate and dibasic lead phosphate),[26] organochlorine compounds,[27,29,30] and pesticides[29–32] have been suggested as human carcinogens and have been linked to an increased risk of pancreatic cancer in previous epidemiological studies.

We did not observe an increased risk of pancreatic cancer for farmers in this study, although farmers typically are exposed to pesticides, which have been linked to an increased risk of pancreatic cancer.[30–32] A possible explanation is that farmers generally have greater physical activity, which has been suggested to reduce the risk of pancreatic cancer.[15,33,34] However, a consistent protective relationship with leisure time activity was not observed in this study (see Table 1).

In this study, men who worked as heavy truck drivers or as railroad brake, signal, and switch operators had an increased risk of pancreatic cancer. Workers in these occupations may be heavily exposed to motor exhaust, which contains polycyclic aromatic hydrocarbons, which have been classified as human carcinogens.[35] An increased risk of pancreatic cancer associated with occupational exposure to polycyclic aromatic hydrocarbons has been suggested by a meta-analysis.[36] Previous epidemiological studies have found an excess of pancreatic cancer risk among truck and bus drivers,[22,37,38] and material moving equipment operators.[11] In this study, we found an increased risk among men who worked in transportation equipment industries. People who worked in such industries also may be exposed to a variety of hazardous materials, such as cutting oils, solvents, and metal dust, which have been suggested as risk factors.[2,12,36,39]

Among women, we observed an increased risk of pancreatic cancer for textile sewing machine operators and tenders, and the risk was greater with longer duration of employment in this occupation (≥10 years). Most previous epidemiological studies reported a positive association between working in textile-related occupations and pancreatic cancer risk among both men and women.[9,10,13,20,40]

An increased risk of pancreatic cancer also was observed in association with employment in furniture and home furnishing stores, as well as among teachers, purchasing agents and buyers, supervisors of sales occupations, and insurance sales people. In the absence of exposure to environmental hazards, lifestyle risk factors, such as lack of physical activity,[15,33,34] may play a role in the development of pancreatic cancer among these workers. Also, it is possible that exposure to infectious agents may play a role in the development of pancreatic cancer

because these jobs involve extensive personal contacts.

The highly aggressive nature of the disease creates methodological challenges. For example, most previous studies relied upon death certificates, which may lead to disease misclassification.[41] An earlier study by Garabrant et al.[30] showed that use of histologically confirmed pancreatic cancer cases to assess the relationship between 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (ie, DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (ie, DDD), and 1,1-dichloro-2,2-bis(p-ethylphenyl)ethane (ie, ethylan) and pancreatic cancer risk produced a much stronger measure of association than use of partially histologically confirmed cases. A lack of information on specific chemical agents in most studies, including this one, also may have contributed to the conflicting results. A variety of chemical agents are involved in different chemical industries, and subjects who worked in these industries may have been exposed to very different levels of these agents.

One of the strengths of this study is that we used histologically confirmed, incident pancreatic cancer cases to reduce disease misclassification. Another strength is the population-based study design with relatively high response rates from both cases and control subjects, which minimizes the potential for selection bias. We included only jobs for which people had been employed for at least 5 years to minimize the potential for recall bias. Detailed information on lifetime job exposure history and major potential confounding factors suggested by previous studies were also collected and controlled for in this study; therefore, confounding is an unlikely explanation for the observed associations.

Like most of the earlier studies of pancreatic cancer, the current investigation relied primarily on surrogates to report the occupational history because of the rapidly fatal nature of the disease. Proxy respon-

dents, particularly spouse and children, generally provide accurate responses for broad categories of exposure information, such as smoking, dietary intake, alcohol consumption, and jobs of longer duration.[42] It has been reported that the level of agreement between proxies and self-reporting respondents improved substantially for reporting jobs held for more than 3 years.[43] A high proportion of spouses and child respondents among proxies of cases (85%) and controls (87%) and inclusion of long-term employment (at least 5 years) only in this study tend to reduce the potential bias resulting from the proxy respondents. In addition, results from several previous studies showed that industries and occupations reported by subjects or next-of-kin are in good agreement with industry records.[44–47] Finally, several of our findings are consistent with the majority of previous epidemiological studies, including studies of transportation-related occupations and textile workers, indicating that information bias is an unlikely explanation for the observed associations.

Using mailed questionnaires instead of face-to-face interviews to collect information on job history may introduce potential exposure misclassification. However, any misclassification of exposure is likely to be non-differential, since subjects had no knowledge of the study hypothesis. Thus, the true associations would be underestimated.[48] Because of the multiple statistical comparisons resulting from numerous categories of industries/occupations and the relatively small number of exposed cases, some observed associations would be expected by chance alone.

In summary, in this population-based case–control study we observed an increased risk of pancreatic cancer associated with employment in several industries (chemical, transportation equipment, communications, railroad transportation, trucking and warehousing, as well as furniture and home furnish-ing stores), and occupations (heavy truck drivers, railroad brake, signal, and switch operators, purchasing agents and buyers, teachers, supervisor of sales occupations, insurance sales, and textile sewing machine operators and tenders). These associations warrant further investigation.

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